New Hepatocellular Carcinoma Therapies

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Overview
This activity is designed to inform physicians about emerging therapies for patients with hepatocellular carcinoma.

Target Audience
This activity is directed toward medical oncologists, primary care physicians, nurses, and nurse practitioners who treat and/or manage patients with hepatocellular carcinoma. Surgical oncologists, radiation oncologists, pathologists, internists, fellows, physician assistants, and other healthcare providers are also invited to participate.

Learning Objectives
After participating in this CME/CE activity, learners should be better prepared to:

- Explain the key unmet needs in the treatment of hepatocellular carcinoma (HCC)
- Describe studies with novel therapeutic agents like c-MET inhibitors, checkpoint inhibitors, and immunotherapeutic vaccines
- Discuss the limited success in validating efficacy with combination therapies in HCC

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Introduction

Background

Hepatocellular cancer (HCC) is the sixth-most prevalent cancer worldwide and accounts for over 745,000 deaths a year.[1] Rising incidences are likely due to several factors including the hepatitis C and obesity epidemics.[2] Median overall survival for advanced HCC is less than 12 months and there remains an urgent need for more effective treatments.[3] A diagnosis of early stage HCC has proven to be very difficult because of the coexistence of inflammation and cirrhosis and the absence of pathognomonic symptoms. At the time of diagnosis, most HCC cases are locally advanced and/or distant metastatic, which results in a difficulty to be treated and poor prognosis. This is true for approximately 40% of patients with HCC.[4] For advanced HCC, systemic therapy is frequently implemented. In recent years, clinical studies and observations have often reported about systemic therapy of advanced HCC, including molecular target therapy, systemic chemotherapy and immunotherapy.[5]

Surgical resection, radiofrequency or microwave ablation, and liver transplantation comprise the mainstay of treatment for early disease offering a chance of cure; however, only 30% to 40% of patients with HCC are suitable for these treatments.[6,7] Loco-regional treatment may be an option for intermediate or advanced HCC. The standard loco-regional treatment for intermediate stage HCC is with trans-arterial chemoembolization (TACE).[8] Although TACE can lead to sustained disease control for intermediate stage HCC,[9] only 20% of patients with HCC are eligible for this therapy.[4] An alternative to TACE is transarterial radioembolization (TARE) using β-emitting yttrium-90 (Y-90). A retrospective study examined the efficacy and safety of TACE versus TARE for unresectable HCC. Meta-analysis indicated that overall survival (OS) was significantly better in the TARE group than the TACE group (HR = 0.74; 95% CI: 0.61-0.90; *P* = .002).[8] Additional outcomes, such as time to progression (TTP), hospitalization time days, and clinical complications, were significantly improved in the TARE group compared with the TACE group.[8] TARE results in similar OS to sorafenib (13.1 vs 11.2 months, respectively) in the treatment of HCC complicated by portal vein thrombosis (PVT).[10] In a retrospective study, it has even been suggested that TARE is more advantageous than sorafenib in PVT with median OS 26.2 versus 8.7 months, respectively (P=.054).[11] The use of TARE with Y-90 in patients with HCC is promising, but further well-designed trials are needed given the paucity of randomized trial data.

For patients requiring systemic therapy, sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), remains the only systemic therapy that is approved in the United States and the European Union for patients with HCC. Sorafenib is effective in advanced HCC offering marginal survival benefit without significant improvement in cancer related symptoms or quality of life.[7] The US and EU basis of approval was in part based on the efficacy and tolerability of sorafenib as demonstrated in the phase III SHARP (Sorafenib HCC Assessment Randomized Protocol) trial.[7] The SHARP trial was performed in 602 European, American and Australian patients with advanced HCC and no history of previous systemic therapy. Subjects were randomized to receive either sorafenib 400 mg bid (n=299) or placebo (n=303). The median OS demonstrated a significant advantage in the sorafenib group over the placebo group (OS 10.7 vs 7.9 months; HR = 0.69; 95% CI, 0.55-0.87; *P* < .001).[7] Median TTP was also longer in sorafenib-treated patients than in those who received placebo (5.5 vs 2.8 months, respectively; HR = 0.58; 95% CI, 0.45-0.74; *P* <.001). There was no significant difference between the sorafenib and placebo group in the median time to symptomatic progression (4.1 vs. 4.9 months, respectively; HR 1.08; 95% CI, 0.88-1.31; *P* = .77). The study was stopped early in view of an early efficacy signal, and patients in the placebo group were offered sorafenib. The most common side effects with sorafenib were diarrhea, weight loss, and hand-foot skin reactions.[7] A large phase III trial in the Asian-Pacific region supported sorafenib efficacy in first-line HCC. Patients treated with sorafenib led to a median OS of 6.5 months compared with 4.2 months in the placebo arm (HR = 0.68; 95% CI, 0.50-0.93; *P* = .014).[12]

First-line Treatment

Sorafenib remains the only approved systemic therapy in the United States and the European Union for patients with HCC, and as previously mentioned, demonstrates significant improvement in OS compared to placebo in first-line HCC.[7] Sorafenib has recently been examined in combination therapies. Although the combination of sorafenib plus doxorubicin showed initial promise when compared with doxorubicin monotherapy, this benefit was lost when the combination therapy was compared to sorafenib monotherapy. In a phase II study, the combination therapy demonstrated having greater median TPP, OS, and progression-free survival compared to doxorubicin alone.[20] However, sorafenib plus doxorubicin did not improve overall or progression-free survival compared to the sorafenib monotherapy in patients with HCC (CALGB 80802).[21]

Recently positive topline results were announced in a phase 3 trial (Study 304) on lenvatinib in the first-line treatment of patients with unresectable HCC.[22] Patients (n=954) were randomized to receive lenvatinib 12 mg or 8 mg qd, depending on body weight (n=478), or sorafenib 400 mg bid (n=476). The primary endpoint was achieved, with lenvatinib showing non-inferiority to sorafenib in OS. Common AEs in the lenvatinib arm were hypertension, diarrhea, decreased appetite, weight loss, and fatigue.[22]

The combination of oxaliplatin and fluorouracil/leucovorin (FOLFOX4) demonstrated mixed improvement results over doxorubicin. The phase III EACH trial, conducted in China, Taiwan, Korea, and Thailand, consisted of 371 randomly assigned patients with advanced HCC to receive either FOLFOX4 or doxorubicin.[23] There was a trend towards improved outcomes with FOLFOX4 (ie, median OS was 6.4 months for FOLFOX4 and 4.97 months for doxorubicin, $P = .07$).[23] When Chinese patients (n=279) were examined in a subgroup analysis of the EACH study, efficacy was demonstrated.[24] Median OS at the prespecified time point of treatment was 5.7 months with FOLFOX4 and 4.3 months with doxorubicin (HR, 0.74; 95% CI, 0.55-0.98; $P = .03$).[24] Hematological toxicity was more frequently reported in the FOLFOX4 group in the Chinese patient subgroup analysis.

Second-line Treatment

A new therapeutic target in HCC is the tyrosine kinase receptor for the hepatocyte growth factor (HGF), encoded by the MET gene, known to promote tumor growth and metastasis in many human organs. The HGF/MET axis has also been shown to promote angiogenesis.[25] Over-expression of MET has been observed in nearly a quarter of HCC cases and there is some evidence to suggest MET expression is a poor prognostic marker. 4 Biomarker data from the SHARP trial revealed that HGF levels correlated with tumor size.[26]

There are recent developments and studies with the selective non-ATP competitive c-MET inhibitor tivantinib. In a phase II study, tivantinib did not offer a survival advantage in patients with advanced HCC. However, post study sub-group analysis revealed that the OS was longer in patients with high baseline expression of c-MET (OS was 7.2 months for tivantinib and 3.8 months for placebo; HR = 0.38; $P = .01$).[27] High baseline expression was defined as samples that scored at least 2+ in at least 50% of tumor cells. As a result of this insight, a phase III trial for patients with tumors over-expressing c-MET in the second-line setting was conducted (METIV trial; NCT01755767). Results from this study were recently reported; tivantinib failed to improve OS compared to placebo.[28] However, recently, questions surrounding tivantinib's specific activity against MET have been raised. Studies demonstrated that tivantinib can act independently of MET, and behaves as a cytotoxic agent rather than a targeted drug. [29,30] This does not mean the drug is ineffective, but that the mechanism of action could be different than originally hypothesized. Cell cycle analysis in non¬–small cell lung cancer cell lines demonstrated that tivantinib induced a G2/M arrest and induced apoptosis.[31] In addition to tivantinib, other c-MET agents that are currently being studied are cabozantinib, INC280, and LY2875358.[13] Both INC280 (NCT01737827) and LY2875358 (NCT01287546) are in the early stages of development (phase I/II). Cabozantinib, a dual inhibitor of MET and VEGFR2, has shown promise in being able to suppress tumor growth in vivo and in vitro.[32] Additionally, a phase II study on cabozantinib exhibited clinical activity in patients with advanced HCC. The overall disease control rate (partial response plus stable disease) at week 12 was 68%.[33] Cabozantinib is currently being investigated in a phase III trial (NCT01908426). A notable difference between this study and the phase III trial of tivantinib is that this cabozantinib study does not screen participants according

TABLE. First and Second-line Clinical Trials That Failed to Demonstrate Significant Efficacy

Line of treatment	Study	Drugs	Patients (N)	Median OS (months)	HR	P value	Ref
1L	BRISK-FL	Brivanib vs sorafenib	577 578	9.5 9.9	1.06	0.31	[14]
2L	BRISK-PS	Brivanib vs placebo	263 132	9.4 8.2	0.89	0.33	[15]
1L	LIGHT	Linifanib vs sorafenib	514 521	9.1 9.8	1.04	0.52	[16]
1L	SEARCH	Sorafenib/ erlotinib vs sorafenib/ placebo	362 358	9.5 8.5	0.92	0.48	[17]
1L	EVOLVE-1	Everolimus vs placebo	362 184	7.6 7.3	1.05	0.68	[18]
1L	REACH	Ramucirumab vs placebo	277 276	9.2 7.6	0.87	0.14	[19]

HR indicates hazard ratio; OS, overall survival; Ref, reference

to the c-MET expression.

The multikinase inhibitor agent, regorafenib, was studied in the RESORCE trial. This randomized, double-blind, placebo-controlled, multicenter phase III study was conducted in patients with second-line HCC. Patients enrolled were adults with HCC who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function. A total of 573 patients were randomized in a 2:1 ratio to receive either regorafenib (160 mg qd) plus best supportive care or placebo plus best supportive care for the first 3 weeks of each 4-week cycle. Patients were followed up for tumor assessments every 6 weeks for the first 8 cycles and every 12 weeks thereafter during treatment. Regorafenib had a median OS of 10.6 months versus 7.8 months for placebo plus best supportive care (HR = 0.62; 95% CI, 0.50-0.78; $P < .001$). Safety and tolerability were generally consistent with the known profile of regorafenib. The AEs that occurred more frequently in the regorafenib group compared with the placebo group were hypertension, hand and foot skin reactions, fatigue, and diarrhea.[34] With the observed increase in OS from the RESORCE trial, this creates a therapeutic sequence of systemic therapy, a combination of sorafenib and regorafenib in sequence, with a median OS of 26 months.

ADI-PEG-20 (pegylated arginine deiminase), an arginine degrading enzyme, and FOLFOX each exhibit clinical activity in patient subsets with HCC. A single center phase I study examined the safety and tolerability of mFOLFOX6 and ADI-PEG-20 in treatment-refractory advanced GI tumors. Treatment-related grade ≥ 3 laboratory AEs occurred in 47% of patients, including neutropenia (n=4), thrombocytopenia (n=3), anemia (n=2), lymphocytopenia (n=2) and hyponatremia (n=1). No dose limiting toxicities, treatment-related deaths, or cases of hepatic failure were observed.[35] Additional evaluations of this combination are necessary in patients with advanced HCC.

The use of checkpoint inhibitors is a novel treatment approach to HCC, and studies using these inhibitors are ongoing in both first- and second-line HCC. Inhibiting the programmed cell death protein 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) pathway activates the immune response to attack tumor cells. PD-1 inhibitors block the binding of PD-L1 to PD-1, enabling T-cell activation. Patients with tumors that over-express PD-L1 are associated with a poorer prognosis.[13] Nivolumab works to block PD-L1 from binding to PD-1. A phase I/II dose-escalation study (CheckMate 040; NCT01658878) in both sorafenib naïve and experienced patients with HCC received 0.1- 10 mg/kg nivolumab intravenously for up to 2 years.[36] The phase I dose-escalation primary endpoint was to examine safety and tolerability. The phase II dose-expansion primary endpoint was objective response rate (ORR). Updated interim analyses indicated that 262 patients have been treated. Responses were evaluable in 214 patients, 20% of patients had an ORR with a duration of response of 9.9 months. The OS rate at 9 months was 74% (95% CI, 67-79).[37] The dose-escalation phase indicated treatment-related AEs included pruritus (19%), rash (23%), diarrhea (10%), and decreased appetite (10%), and laboratory treatment-related AEs included increased aspartate aminotransferase, alanine aminotransferase, lipase, and amylase (21%, 15%, 21%, and 19%, respectively).[37] This study highlights the importance of testing anti-PD-L1 in both first- and second-line settings.

Other investigational PD-1/PD-L1 inhibitors include pembrolizumab and durvalumab. Pembrolizumab is being examined in a randomized, double-blind, placebo-controlled phase III KEYNOTE-240 study (NCT02702401). The aim is to compare the efficacy and safety of pembrolizumab plus best supportive care versus placebo pembrolizumab plus best supportive care in patients with previously treated advanced HCC. The estimated study completion date is February 2019. Another class of checkpoint inhibitors being investigated for HCC are CTLA-4 inhibitors (ie, tremelimumab and ipilimumab). Although tremelimumab was demonstrated to have a good safety profile, the incidence of side effects with an anti-CTLA4 antibody has been reported to be higher than with an anti-PD-1 antibody.[38] There is an ongoing phase I/II trial aimed at evaluating the safety, tolerability, and antitumor activity of durvalumab in combination with tremelimumab, and as monotherapies in patients with unresectable HCC (NCT02519348).[39]

The development of genetically engineered oncolytic viruses are a relatively new approach to HCC treatment. An oncolytic virus is a genetically engineered or naturally occurring virus that can selectively replicate in and kill cancer cells without harming the normal tissues.[40] The problem with oncolytic virus development was not getting the virus to replicate in cancer cells, instead ensuring the virus that would not replicate in normal cells. To overcome this challenge and create a cancer cell-specific virus, scientists can select a virus that is non-virulent in humans or by engineering the virus genome. To date, two genetically engineered oncolytic viruses have been approved for marketing as drugs: Oncorine (H101) for head and neck cancer and esophagus cancer and T-VEC (talimogene laherparepvec) for melanoma.[40]

JX-594 (pexastimogene devacirepvec, Pexa-Vec) is a genetically engineered vaccinia virus that has a mutation in the thymidine kinase (TK) gene. JX-594 has an insertion of human granulocyte-macrophage colony stimulating factor (GM-CSF) and lacZ transgenes in the TK locus, which stimulates the anti-tumor immune response.[41] There have been a number of clinical studies which provide details into the safety and efficacy of JX-594. Phase I data supports JX-594 as well tolerated with the dose-limiting toxicity being hyperbilirubinemia,[42] and the

possibility of intravenous delivery through a dose-escalation study.[43] A dose-finding phase II study was performed in patients with HCC, in which a high-dose and low-dose JX-594 were used. The median OS was significantly longer in the high dose arm compared with the low dose arm (14.1 vs 6.7 months, respectively).[44] A phase III trial in patients with advanced stage HCC began enrolling patients in late 2015 (PHOCUS, NCT02562755). In this trial, JX-594 will be administered 3 times bi-weekly at days 1, 15, and 29, followed by sorafenib at day 43, whereas, in the control arm, sorafenib begins day 1 at 400 mg twice daily (NCT02562755).[45]

Combination Local Plus Systemic Therapies

There is promising research being conducted on combination therapies, local plus systemic therapies. Currently, there are a number of combination therapies tested in patients with HCC that failed to demonstrate beneficial clinical outcomes. For example, the combination of TACE with doxorubicin-eluting beads (DEB-TACE) and sorafenib was explored in the phase II trial (SPACE trial) in patients with intermediate HCC. Patients (n = 307) were randomized 1:1 to received DEB-TAC (150 mg doxorubicin) plus sorafenib (400mg bid) or DEB-TACE plus placebo. There was no significant difference in the time to progression (TTP) for either the sorafenib/DEB-TACE or placebo/DEB-TACE group (169 vs 166 days, respectively; HR, 0.797; P = .072).[46] However, there are many investigational trials that may improve our understanding of how local therapy may be safely and efficaciously combined with systemic therapy.

There are a number of ongoing combination studies in which local plus systemic therapies are being tested. The Sorafenib and Micro-therapy Guided by Primovist Enhanced MRI in Patients With Inoperable Liver Cancer (SORAMIC; NCT01126645) study evaluates sorafenib with combination with selective internal radiation therapy (SIRT) or sorafenib alone. Initial safety analysis shows similar toxicity at 8.3 months between the two arms.[47] The SorAfenib versus Radioembolisation in Advanced Hepatocellular carcinoma (SARAH; NCT01482442) trial is the first prospective head-to-head randomized controlled trial of Y-90 resin microspheres versus sorafenib in advanced HCC.[48] Similarly, the Singapore-based phase III head-to-head randomized controlled trial also aimed to examine sorafenib versus resin microspheres in 360 patients with advanced HCC (SIRveNIB; NCT01135056). The primary endpoint for both the SARAH and SIRveNIB trials is OS and results are expected soon. Immune checkpoint inhibitors could be particularly effective for the treatment of inflammation induced by TACE or radiofrequency ablation (RFA).[49] A clinical trial of adjuvant therapy with anti-CTLA-4 antibody, tremelimumab, after TACE is underway. The results of the interim analysis demonstrated that tremelimumab in combination with TACE was safe and feasible.[50]

Although there have been limited success in validating efficacy with combination therapies in HCC, there are many combinations that have yet to be tested. Further studies are warranted to evaluate combination therapies, along with novel therapeutic targets. These future studies are important to improve treatment benefits for patients with HCC.

Ghassan K. Abou-Alfa, MD, Medical oncologist at the Memorial Sloan Kettering Cancer Center, offered his insights on current and emerging treatment approaches in patients with hepatocellular carcinoma.

Moderator: What would you describe as some of the unmet needs in the treatment of hepatocellular carcinoma (HCC)?
Dr. Abou-Alfa: The greatest unmet need is the lack of therapies available for patients with HCC. Sorafenib remains the sole FDA approved drug for HCC. Lenvatinib was recently shown to be non-inferior to sorafenib in terms of OS for first-line HCC. Even with the news on lenvatinib and recent positive data on regorafenib in second-line HCC, there remains few options for patients in terms of therapies for treatment. Considering HCC is a fatal disease with limited survival and therapeutic agents provide limited improvements in patient outcomes, treatment options remain the greatest unmet need in this area.

Moderator: What are some of the most significant recent developments in the loco-regional treatment for HCC?
Dr. Abou-Alfa: The advent of local HCC therapy has been evolving for the last 17 years, since the year 2000. The main focus has been on embolization with chemotherapeutic drugs or without. However, recent advances include the use of yttrium-90 (Y-90) radioembolization, as examined in multiple studies. There are a couple of ongoing clinical trials examining the role of Y-90 radioembolization in advanced HCC. Patients with advanced loco-regional disease could benefit from local therapy versus systemic therapy.

There is another development of adjoining therapies or adjuvant therapies that could be given with local therapy to enhance outcomes. The first effort has been with the combination of chemoembolization or trans-arterial chemoembolization (TACE) plus sorafenib. Several clinical trials have been performed thus far, among which is the phase II SPACE study from Lencioni et al. (2016) examining the use of chemoembolization plus sorafenib versus chemoembolization alone. The SPACE study did not show an improvement in outcome; however, that does not mean the community should abandon the idea of combining local plus systemic therapy. There are a number of ongoing clinical trials investigating TARE in patients with advanced HCC, including the phase III SARAH study, phase II SORAMIC study, and phase III SIRveNIB study. I believe that there is a critical role that immunotherapy might play in that field, and combining chemoembolization

plus an immune-oncologic will deserve a look by the scientific community.

In a phase III study, the PHOCUS study, is evaluating an investigational drug called Pexa-Vec (JX-594), in combination with sorafenib versus sorafenib alone, to determine if it can slow the progression of HCC. Pexa-Vec (JX-594) is an attenuated vaccinia virus engineered to stimulate anti-tumor immunity and directly lyse tumor cells. Pexa-Vec has enhanced cancer selectivity through the deactivation of its thymidine kinase (TK) gene, and it has been engineered to express the granulocyte-macrophage colony stimulating factor (GM-CSF) gene to stimulate a systemic anti-tumor immune response. The results of the PHOCUS trial could be a significant development in the loco-regional treatment of HCC.

Moderator: The phase III randomized study CALGB 80802 (Alliance) evaluated sorafenib plus doxorubicin versus sorafenib in patients with advanced HCC. What are the key findings from this study and the clinical implications of these findings?
Dr. Abou-Alfa: CALGB 80802 study was based on the randomized phase II study of sorafenib plus doxorubicin versus sorafenib that showed a promising improvement in survival for the sorafenib plus doxorubicin, reaching 13.7 months. Based on the phase II outcome, CALGB 80802 was initiated.

The three key findings from this study were, first, the study was unfortunately negative. The combination of the sorafenib plus doxorubicin did not fare any better than sorafenib alone. The median survival of the patients on the sorafenib plus doxorubicin arm 8.9 months vs. 10.5 months for sorafenib alone (HR, 1.06; 95% CI, 0.8-1.4; $P = .24$). As a result, I would not recommend this combination as a therapeutic intervention.

Second, this study poses a question about the role of doxorubicin with regard to local plus systemic therapy. Our previous work, 51 we compared chemoembolization with doxorubicin versus bland embolization without doxorubicin. Our conclusion was there was not difference between these two treatment arms. This raises the question of the specific role of doxorubicin in HCC therapy.

Lastly, the CALGB 80802 study was an important collaboration among all the cooperative groups under the direction of the National Cancer Institute (NCI). It proves that our community of experts in the US and Canada are paying attention to the disease, addressing unmet needs, and capable of finishing large phase III studies in HCC. As the incidence of HCC continues to rise, it is important for our cooperative groups to continue in these efforts.

Moderator: Do c-MET inhibitors such as tivantinib and cabozantinib have a role in the treatment of HCC? Do we have any clinical trial data that is promising for these agents?
Dr. Abou-Alfa: There is no doubt that this was the hot topic item before immunotherapy came on board. The benefit of c-MET inhibitors has been demonstrated in two phase II trials for both tivantinib and cabozantinib. These trials showed an improvement in outcome in the second-line setting, after failure with sorafenib. Cabozantinib has shown the overall disease control rate (partial response plus stable disease) at the 12th week was 68%. 33 Tivantinib has shown an improvement in median OS, about 7.2 months in the c-MET-high expression patients, compared to 3.8 months OS in the placebo c-MET-high patient months. The patients defined as c-MET-high had tissue samples which scored at least a 2+ in at least 50% of tumor cells to be regarded as having high MET expression.

Currently, there are two phase III trials in patients diagnosed as c-MET high in tumor sample.

One trial is with tivantinib in c-MET-high patients based on the phase II data that indicates c-MET is probably a prognostic marker, or even a predictive marker if evaluated. This trial has completed enrollment and results are pending (NCT01755767). The other trial is with cabozantinib, and is still accruing patients (NCT01908426), and does not screen and randomize patients based on c-MET expression. I am honored to lead this effort. We'll evaluate patient's c-MET expression even though it is not the primary focus of the study. These studies will be important in defining what role c-MET inhibitors play in this HCC.

Moderator: Phase 3 RESORCE trial results showed survival advantage with regorafenib. What likely impact will data from this trial have in the treatment of HCC?
Dr. Abou-Alfa: Few experts expected a multi-tyrosine kinase drug like regorafenib to overcome the resistance of the similar tyrosine-kinase inhibitor sorafenib and demonstrate positive results. Improved survival was close to 11 months in the regorafenib arm versus about 8 months in the placebo arm. Regorafenib is "misunderstood" as being nothing more than sorafenib with minor changes, but it is clear that patients with HCC did benefit despite the progression on sorafenib. This raises the question about what is the advantage that regorafenib presents to tumors, and what kind of stressors these tumors had when they were exposed to sorafenib beforehand?

Other than the improvement in survival, it appears that there was an unplanned analysis of the combined survival for the patients on sorafenib plus regorafenib. The combined median survival of 26 months for sorafenib followed by regorafenib is quite impressive. Although not a validated scientific point, this analysis provides a bit of reference, and provides an interesting concept that deserves to be explored further. The role of regorafenib in the HCC treatment will be interesting, and if an FDA approval occurs, it will be interesting if the drug is restricted to the second-line setting after sorafenib. Time will tell how regorafenib will fit in the treatment paradigm of HCC.

Moderator: What is the rationale supporting the use of checkpoint inhibitors in HCC? Please share some clinical trial data that we have so far for these agents.
Dr. Abou-Alfa: There is great data available supporting the use of checkpoint inhibitors in HCC. Preclinical evidence supports the expression of the PD-L1 and probably CTLA-4 in HCC, as well as in parenchymal cells. Within the diseased liver, excessive inflammation results in the loss of liver tolerogenic mechanisms, promoting further inflammation and leading to clinical consequences as serious as organ failure. The response rates when checkpoint inhibitors are utilized have been reported to be 20% in some studies. Currently, key checkpoint inhibitors being studied are nivolumab versus sorafenib in the first-line setting. CheckMate 459 study (NCT02576509) is an ongoing, open-label, phase 3 study to investigate the effect of the PD-1 inhibitor nivolumab versus sorafenib as a first-line treatment in advanced HCC. The outcome of this study could change the approach to HCC treatment. Nivolumab could define immunotherapy as being the appropriate approach to HCC in the first-line setting. Pembrolizumab is being examined in the second-line HCC. There is an ongoing randomized phase I/II trial evaluating the combination of durvalumab plus tremelimumab versus tremelimumab monotherapy versus durvalumab monotherapy in the second-, first-line setting. Checkpoint inhibitors carry a lot of promise, but they have to deliver positive outcomes in clinical trials. We have to see survival improvement before we claim that checkpoint inhibitors really are appropriate.

Moderator: What role do you see of immunotherapeutic vaccines in HCC treatment? Would you be able to provide a brief overview of the PHOCUS trial and rationale for this trial?
Dr. Abou-Alfa: The phase III PHOCUS trial evaluates JX-594 in combination with sorafenib versus sorafenib alone. There are three important things to know about JX-594. It is an attenuated vaccinia virus engineered to stimulate anti-tumor immunity and directly invade cancer cells. Additionally, JX-594 has been engineered to express GM-CSF to stimulate an anti-tumor immune response. Lastly, the investigational drug would cap blood supply to the tumor, suppressing tumor growth. The results of the PHOCUS trial could be a significant development in the loco-regional treatment of HCC.

Moderator: How important is multidisciplinary care in the treatment of patients with HCC including those with viral hepatitis and HCC?
Dr. Abou-Alfa: Multidisciplinary care is evolving. Data supports that patients who are seen by multiple different specialties will have better outcomes. El-Serag and colleagues (2011) provided great HCC surveillance recommendations.[52] I think the paradigm is shifting towards more multidisciplinary approaches, transitioning the patient from one specialty to another in order to best benefit the patient. It is strongly encouraged that physicians are part of a multidisciplinary team to optimize the outcome for their patient. This is how we can move the HCC field forward.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-E386. doi: 10.1002/ijc.29210.
2. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology.* 2016; pii: S0016-5085(16)35389-6. doi: 10.1053/j.gastro.2016.11.020.
3. Fong ZV, Tanabe KK. The clinical management of hepatocellular carcinoma in the United States, Europe, and Asia: a comprehensive and evidence-based comparison and review. *Cancer.* 2014;120(18):2824-38. doi: 10.1002/cncr.28730.
4. Giordano S, Columbano A. Met as a therapeutic target in HCC: Facts and hopes. *J Hepatol.* 2014;60(2):442-52. doi: 10.1016/j.jhep.2013.09.009.
5. Gong XL, Qin SK. Progress in systemic therapy of advanced hepatocellular carcinoma. *World J Gastroenterol.* 2016;22(29):6582-6594. doi: 10.3748/wjg.v22.i29.6582.
6. Lencioni R, Chen XP, Dagher L, Venook AP. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? *Oncologist.* 2010;15 (suppl 4):42-52. doi: 10.1634/theoncologist.2010-S4-42.
7. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, et al. Sorafenib in advanced hepatocellular carcinoma. [published correction appears in N Engl J Med. 2008;359(4):2497-2499]. *N Engl J Med.* 2008;359(4):378-390. doi: 10.1056/NEJMoa0708857.
8. Zhang Y, Li Y, Ji H, Zhao X, Lu H. Transarterial Y90 radioembolization versus chemoembolization for patients with hepatocellular carcinoma: a meta-analysis. *Bioscience Trends.* 2015;9(5):289–298. doi: 10.5582/bst.2015.01089.
9. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359(9319):1734-1739.
10. Gramenzi A, Golfieri R, Mosconi C, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. *Liver Int.* 2015;35(3):1036-1047. doi: 10.1111/liv.12574.
11. Edeline J, Crouzet L, Campillo-Gimenez B, et al. Selective internal radiation therapy compared with sorafenib for hepatocellular carcinoma with portal vein thrombosis. *Eur J Nucl Med Mol Imaging.* 2016;43(4):635-643. doi: 10.1007/s00259-015-3210-7.

12. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10(1):25-34. doi: 10.1016/S1470-2045(08)70285-7.
13. Thillai K, Ross P, Sarker D. Molecularly targeted therapy for advanced hepatocellular carcinoma - a drug development crisis? *World J Gastrointest Oncol.* 2016;8(2):173–185. doi: 10.4251/wjgo.v8.i2.173.
14. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol.* 2013;31(28):3517-3524. doi: 10.1200/JCO.2012.48.4410.
15. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol.* 2013;31(28):3509-3516. doi: 10.1200/JCO.2012.47.3009.
16. Toh HC, Chen PJ, Carr BI, et al. Phase 2 trial of linifanib (ABT-869) in patients with unresectable or metastatic hepatocellular carcinoma. *Cancer.* 2013;119(2):380-387. doi: 10.1002/cncr.27758.
17. Zhu AX, Rosmorduc O, Evans TR, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2015;33(6):559-566. doi: 10.1200/JCO.2013.53.7746.
18. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA.* 2014;312(1):57-67. doi: 10.1001/jama.2014.7189.
19. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following firstline therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2015;16(7):859-870. doi: 10.1016/S1470-2045(15)00050-9.
20. Abou-Alfa GK, Johnson P, Knox JJ, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA.* 2010;304(19):2154-2160. doi: 10.1001/jama.2010.1672.
21. Abou-Alfa GK, Niedzwieski D, Knox JJ, et al. Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC): CALGB 80802 (Alliance). *J Clin Oncol.* 2016a;34(suppl 4S; abstr 192).
22. Positive topline results of large phase 3 trial show Eisai's Lenvatinib meets primary endpoint in unresectable hepatocellular carcinoma [news release]. Woodcliff, NJ: Eisai, Inc.; January 25, 2017. http://eisai.mediaroom.com/2017-01-25-Positive-Topline-Results-of-Large-Phase-3-Trial-Show-Eisais-Lenvatinib-Meets-Primary-Endpoint-in-Unresectable-Hepatocellular-Carcinoma. Accessed February 16, 2017.
23. Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol.* 2013;31(28):3501-3508. doi: 10.1200/JCO.2012.44.5643.
24. Qin S, Cheng Y, Liang J, et al. Efficacy and safety of the FOLFOX4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the EACH study. *The Oncologist.* 2014;19(11):1169-1178. doi:10.1634/theoncologist.2014-0190.
25. Bussolino F, Di Renzo MF, Ziche M, et al. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. *J Cell Biol.* 1992;119(3):629–641.
26. Llovet JM, Peña CE, Lathia CD, Shan M, Meinhardt G, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res.* 2012;18(8):2290-2300. doi: 10.1158/1078-0432.CCR-11-2175.
27. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol.* 2013;14(1):55-63. doi: 10.1016/S1470-2045(12)70490-4.
28. Daiichi Sankyo and ArQule Announce the Completion of the METIV-HCC Phase 3 Study of Tivantinib in Second-Line Treatment of MET-Overexpressing Hepatocellular Carcinoma. Burlington, MA: Daiichi Sankyo; February 17, 2017. http://dsi.com/documents/10710/267915/Tivantinib+METIV-HCC+-press+release+FINAL.pdf/85d5901d-bd3e-f833-f574-41e655f341a8. Accessed February 23, 2017.
29. Katayama R, Aoyama A, Yamori T, et al. Cytotoxic activity of tivantinib (ARQ 197) is not due solely to c-MET inhibition. *Cancer Res.* 2013;73(10):3087-3096. doi: 10.1158/0008-5472.CAN-12-3256.
30. Basilico C, Pennacchietti S, Vigna E, et al. Tivantinib (ARQ197) displays cytotoxic activity that is independent of its ability to bind MET. *Clin Cancer Res.* 2013;19(9):2381–2392. doi: 10.1158/1078-0432.CCR-12-3459.
31. Calles A, Kwiatkowski N, Cammarata BK, Ercan D, Gray NS, Jänne PA. Tivantinib (ARQ 197) efficacy is independent of MET inhibition in non-small-cell lung cancer cell lines. *Mol Oncol.* 2015;9(1):260-9. doi: 10.1016/j.molonc.2014.08.011.
32. Xiang Q, Chen W, Ren M, et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. [published correction appears in Clin Cancer Res. 2016;22(9):2312]. *Clin Cancer Res.* 2014;20(11):2959-2970. doi: 10.1158/1078-0432.CCR-13-2620.
33. Verslype C, Cohn AL, Kelley RK, et al. Activity of cabozantinib (XL184) in hepatocellular carcinoma: results from a phase

II randomized discontinuation trial (RDT). *J Clin Oncol.* 2012;30:(suppl; abstr 4007).
34. Bruix J, Merle P, Granito A, et al. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma progressing on sorafenib: Results of the international, randomized phase 3 RESORCE trial. ESMO World Congress on Gastrointestinal Cancer. June 29-July 2; Barcelona, Spain. Abstract LBA-03. Presented June 30, 2016. Annals of Oncology (2016) 27 (2): 1-3. 10.1093/annonc/mdw237
35. Harding JJ, Lowery MA, Uhlitskykh K, et al. A phase I study of mFOLFOX6 and ADIPEG20 in patients (pts) with advanced hepatocellular carcinoma (HCC) and other gastrointestinal (GI) malignancies. *J Clin Oncol.* 2017;35(suppl 4S; abstract 384).
36. El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. *J Clin Oncol;* 2015,33(suppl; abstr LBA101). Retrieved from: http://meetinglibrary.asco.org/content/146146-156.
37. Melero I, Sangro B, Yau TC, et al. Nivolumab dose escalation and expansion in patients with advanced hepatocellular carcinoma (HCC): The CheckMate 040 study. *J Clin Oncol.* 2017; 35(suppl4S; abstr 226).
38. Sangro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol.* 2013;59(1):81-88. doi: 10.1016/j.jhep.2013.02.022.
39. Abou-Alfa GK, Sangro B, Morse M, et al. Phase 1/2 study of durvalumab and tremelimumab as monotherapy and in combination in patients with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol.* 2016;34(suppl; abstr TPS3103).
40. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. *Cancer Science.* 2016;107(10):1373–1379. doi: 10.1111/cas.13027.
41. Parato KA, Breitbach CJ, Le Boeuf F, et al. The oncolytic poxvirus JX-594 selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers. *Mol Ther.* 2012;20(4):749-58. doi: 10.1038/mt.2011.276.
42. Park BH, Hwang T, Liu TC et al. Use of a targeted oncolytic poxvirus, JX-594, in patients with refractory primary or metastatic liver cancer: a phase I trial. *Lancet Oncol.* 2008;9(6):533-42. doi: 10.1016/S1470-2045(08)70107-4.
43. Breitbach CJ, Bruke J, Jonker D et al. Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans. *Nature.* 2011;477(7362):99-102. doi: 10.1038/nature10358.
44. Heo J, Reid T, Ruo L et al. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. *Nat Med.* 2013;19(3):329-36. doi: 10.1038/nm.3089.
45. SillaJen, Inc. Hepatocellular Carcinoma Study Comparing Vaccinia Virus Based Immunotherapy Plus Sorafenib vs Sorafenib Alone (PHOCUS). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [2017Jan25]. Retrieved from: https://clinicaltrials.gov/ct2/show/NCT02562755 NLM Identifier: NCT02562755
46. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol.* 2016;64(5):1090–1098. doi: 10.1016/j.jhep.2016.01.012.
47. Ricke J, Bulla K, Kolligs F, et al. Safety and toxicity of radioembolization plus sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. *Liver Int.* 2015;35(2):620–6. doi: 10.1111/liv.12622.
48. Vilgrain V, Abdel-Rehim M, Sibert A, et al. Radioembolisation with yttrium–90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. *Trials.* 2014;15:474. doi: 10.1186/1745-6215-15-474.
49. Kang TW, Rhim H. Recent advances in tumor ablation for hepatocellular carcinoma. *Liver Cancer.* 2015;4(3):176-187. doi: 10.1159/000367740.
50. Duffy A, Makarova-Rusher OV, Pratt D, et al. Tremelimumab, a monoclonal antibody against CTLA-4, in combination with subtotal ablation (trans-catheter arterial chemoembolization (TACE), radiofrequency ablation (RFA) or cryoablation) in patients with hepatocellular carcinoma (HCC) and biliary tract carcinoma (BTC). *J Clin Oncol.* 2016;34(suppl; abstr 4073).
51. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol.* 2016;34(17):2046-2053.
52. El-Serag HB, Davila JA. Surveillance for hepatocellular carcinoma: in whom and how? *Therap Adv Gastroenterol.* 2011;4(1):5-10. doi: 10.1177/1756283X10385964.